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Diabetic Hyperglycemic Emergencies: A Systematic Approach

Abstract

For patients presenting with suspected diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS) understanding of the etiology and pathophysiology will ensure optimal emergency management. Morbidity and mortality is most often due to the underlying precipitating cause, which may include infection, infarction/ischemia, noncompliance with insulin therapy, pregnancy, and dietary indiscretion. Current guidelines are based primarily on expert opinion and consensus statements, but more recent evidence suggests that recommendations related to arterial blood gas, insulin bolus, and IV fluid replacement should be re-evaluated. This issue presents an approach to DKA and HHS management based on current evidence, with a simplified pathway for emergency department management.

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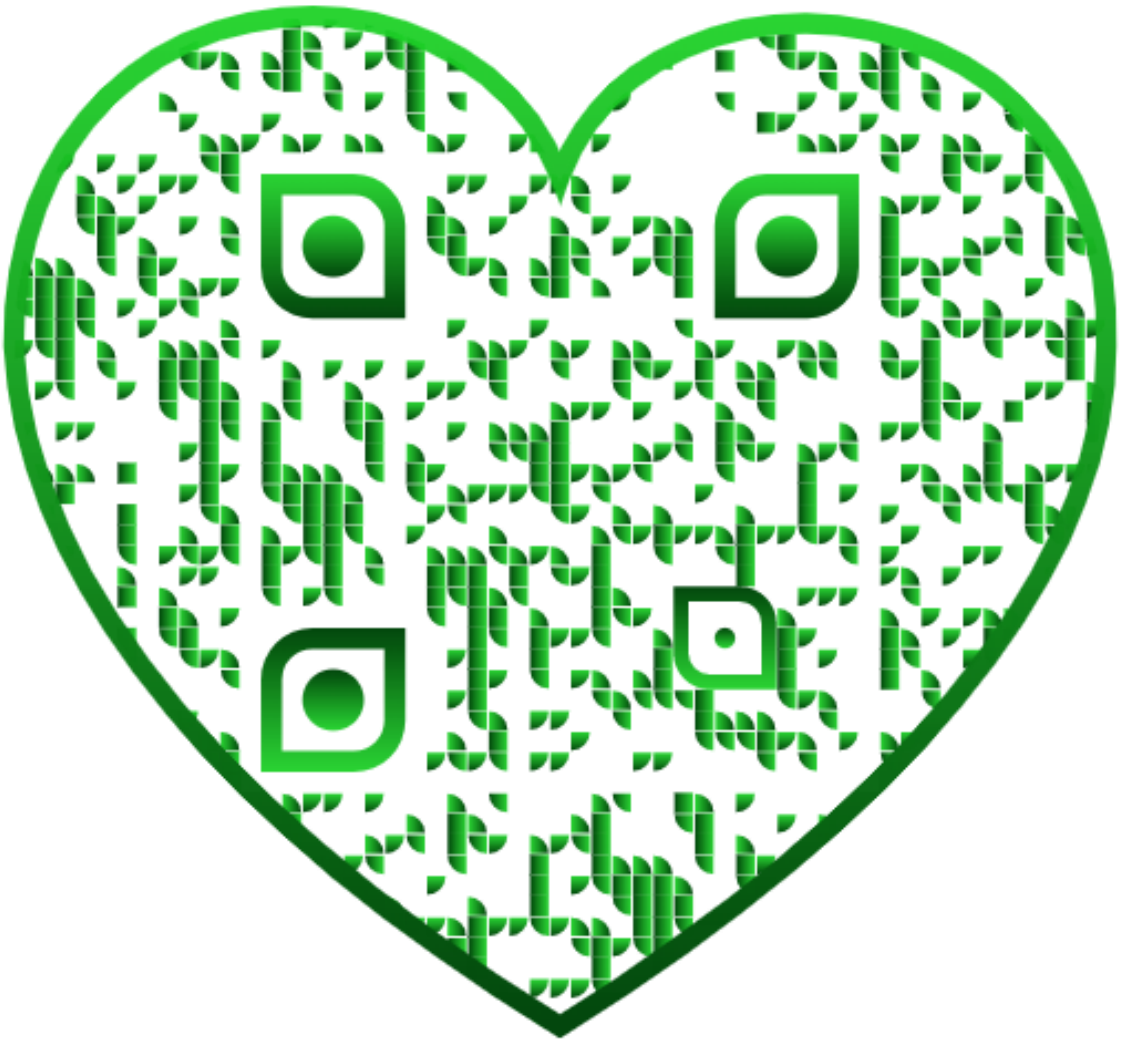

Case Presentations

Midway through your shift, a 23-year-old woman arrives by EMS. She is ill-appearing, tachypneic, and has a distinct odor you recognize as ketones. Her bedside glucose is 680 mg/dL. You suspect DKA, but wonder what led to it. You know that starting insulin and fluids is indicated, but you wonder whether insulin should be administered as an IV bolus, whether insulin should be given before or after IV fluids, what fluids are most appropriate, or whether you should just proceed with subcutaneous insulin. As if these questions were not enough, your first-year resident tells you the patient has a pH of 7.1 and asks if she needs sodium bicarbonate. He also asks if she should be intubated, since she is breathing so hard…

A 76-year-old man arrives with his wife via EMS. He is slow to respond to you, and his wife says that over the past 10 days he has become increasingly weak, stopped walking, and this morning would not talk to her. His vital signs are: blood pressure, 90/60 mm Hg; pulse, 110 beats/min; and respiratory rate, 16 breaths/min. He is afebrile and has an oxygen saturation of 96% on room air. A fingerstick glucose reads high, and a venous pH is 7.38. You wonder whether his initial therapy should be similar to that for DKA, even with his normal pH, and whether 0.45% saline is the ideal fluid in his hyperosmolar state…

A 30-year-old man presents in DKA. He is a known type 1 diabetic and has an insulin pump that he says has been alarming. He is awake, alert, and his triage vital signs are: blood pressure, 110/60 mm Hg; pulse, 121 beats/min; respiratory rate, 26 breaths/min, temperature, 35.6°C (96°F); and oxygen saturation, 100% on room air. His fingerstick glucose reads high, and his venous pH is 7.12. You turn off his insulin pump and begin him on "standard therapy" of an IV fluid bolus of 20 mL/kg of normal saline followed by 500 mL/hr, 6 units of regular insulin IV, and put him on an insulin drip of 6 units/hr. The patient's vital signs begin to stabilize, with his blood pressure rising and pulse and respirations slowing towards normal. Three hours after ED entry, the patient has a cardiac arrest and is defibrillated out of torsades de pointes. You wonder what went wrong …

Introduction

As the incidence of diabetes has risen over the past several decades, so too have the number of patients who present to the emergency department (ED) with diabetes-related emergencies, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).[1] DKA alone is responsible for more than 140,000 hospital admissions per year in the United States, with an average length of stay of 3.4 days. This number has increased by 30% over the past decade.[2,3] In 2014, charges for DKA hospitalization amounted to $5.1 billion.[4] The emergency clinician must be prepared to identify and promptly treat these conditions because, without intervention, morbidity and mortality are high. Being knowledgeable about common precipitants and rapidly identifying their presence is essential, as morbidity is primarily related to the triggering event. The metabolic derangements that occur in these conditions require careful treatment, but the treatment algorithms can seem overly complex. Having a simplified, systematic approach to patients with these conditions will improve efficiency in managing these emergencies.

Unfortunately, consensus statements and guidelines often lag behind recent data. Indeed, the most recent American Diabetes Association (ADA) consensus statement is over 10 years old and thus does not incorporate newer literature that supports changes in practice. This issue of *Emergency Medicine Practice* focuses on the management of the common diabetic hyperglycemic emergencies, DKA and HHS, and provides treatment strategies that are based on the best available evidence.

Critical Appraisal of the Literature

A literature search of PubMed was performed without any date filters using the search terms *diabetic ketoacidosis, DKA, hyperosmolar hyperglycemic state,* and *HHS*. The initial search produced over 2 million results. The majority of the results were review articles, case studies, and expert opinion. Results were narrowed by filtering for clinical trials published in the past 10 years and review articles published in the past 5 years. Consensus statements released by the ADA in 2009 and the International Society for Pediatric and Adolescent Diabetes (ISPAD) in 2018 were also reviewed.[1,5] The ADA and ISPAD guidelines are primarily expert opinion and were developed from studies through their publication years. References used by consensus statements were also evaluated. Final selections were made based on clinical relevance. During the literature search, particular attention was given to prospective studies; however, there are only a few randomized trials evaluating the treatment of DKA and HHS in the ED, and those that do exist tend to be quite small (approximately 50 patients or fewer).[6-8]

Etiology and Pathophysiology

DKA and HHS are 2 distinct entities that exist on a spectrum of hyperglycemic emergencies. DKA typically occurs in younger patients, primarily those with type 1 diabetes (though type 2 diabetics can also develop DKA, particularly when concomitant illness is present). HHS is much more likely to occur in elderly patients with type 2 diabetes who have multiple underlying comorbidities, though it is being diagnosed increasingly in younger adults and even in children. In more than one-third of patients, these conditions overlap.[1]

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Although the exact pathophysiologic mechanisms of DKA and HHS are complex, in general, the pathogenesis begins with insufficient insulin and high levels of counterregulatory hormones (glucagon, cortisol, growth hormone, and catecholamines). This results in hyperglycemia, which promotes an osmotic diuresis, leading to dehydration and electrolyte loss. In both conditions, insulin levels are insufficient for peripheral tissue glucose utilization, resulting in hyperglycemia.

In DKA, there is an absolute insulin deficiency, in which glucose cannot be moved into the cell. To meet the body's energy needs, fats are metabolized into free fatty acids that are then converted in the liver to ketone bodies. The 2 main ketones, beta-hydroxybutyrate and acetoacetate, are both strong acids, and their presence creates a significant metabolic acidosis in DKA.

Whereas there is an absolute insulin deficiency in DKA, in HHS, there is only a relative insulin deficiency. Endogenous insulin production is adequate to prevent a total catabolic state. Therefore, lipolysis, ketone body production, and significant acidosis do not occur; however, there is insufficient insulin to permit tissue utilization of glucose, and thus hyperglycemia still occurs.[1]

In both states, the resultant hyperglycemia creates an osmotic diuresis in which tremendous amounts of water are lost through diuresis. It is estimated that there is a 3-L to 6-L fluid deficit in most adult cases of DKA and a 9-L to 12-L fluid deficit in HHS. In children, water loss is estimated to average 70 mL/kg in DKA and 12% to 15% of body weight in HHS.[5] Fluid losses tend to be greater in HHS for several reasons, including the prolonged course of onset, delay in recognition, and the fact that many of these patients are elderly, bedridden patients with impaired thirst response. At least 20% of patients presenting with HHS have no documented history of diabetes.[1] In addition to fluid loss, osmotic diuresis also causes urinary wasting of electrolytes, resulting in large total body deficits of potassium, magnesium, and phosphate.

Counterregulatory hormones also play a key role in the development of the metabolic derangements seen in these conditions. In both states, there is an increase in cortisol, catecholamines, glucagon, and growth hormone. Together, they promote gluconeogenesis, glycogenolysis, and proteolysis, compounding the development of hyperglycemia.

Precipitating Causes

Both DKA and HHS are usually triggered by a precipitating cause. The major causes of DKA and HHS can be remembered as the "Five Is." **(See Table 1.)**

Identifying underlying causes is critical, as they contribute to morbidity and mortality. Death directly from DKA and HHS is relatively uncommon; instead, patients are much more likely to die from the precipitating event. In DKA, the mortality rate has dropped below 1% since the 1970s, when the mortality rate was reported to be as high as 7% to 10%.[2] HHS mortality rates are much higher, in the 5% to 20% range. In both conditions, risk of death is much higher at the extremes of age.[1] In patients presenting with DKA or HHS, consider the following 5 "I"precipitating causes:

- **Infection:** Common infectious sources include urinary, respiratory, and dermatologic systems.
- **Infarction:** Infarction of any tissue can promote development of hyperglycemic emergencies, including heart (myocardial infarction), brain (stroke), and bowel.
- **Infant (pregnancy):** Pregnant patients have higher insulin requirements during pregnancy due to increased levels of insulin-antagonistic hormones that lead to higher insulin resistance. Pregnancy testing should be performed on all women of childbearing age. Insulin requirements during pregnancy vary throughout trimesters and are also variable by type 1 and type 2 diabetes. In the first trimester, type 1 diabetics need less insulin, whereas type 2 diabetics need more. In the second and third trimesters, both type 1 and type 2 diabetics need higher insulin doses.[9]
- **Indiscretion of diet:** Noncompliance with diet and failure to use adequate correction doses of insulin may precipitate hyperglycemic crises. Eating disorders are also being increasingly recognized as a cause, especially in young patients with recurrent DKA.[1]
- **Insulin deficiency:** Recent data suggest that omission of insulin is likely overtaking infection as the most common precipitant of DKA in developed countries.[3] This is a particular problem among teenagers and is the most common cause in recurrent cases.

There are numerous other causes of DKA/HHS, including medications, pancreatitis, and thyrotoxicosis. Finally, while DKA typically occurs in type 1 diabetics with an underlying precipitating cause,

Table 1. "Five Is" Precipitating Diabetic Ketoacidosis/Hyperosmolar Hyperglycemic State

Precipitant	Specific Examples
Infection	Pneumonia, urinary tract infection, skin infections
Infarction	Myocardial infarction, stroke, bowel infarction
Infant on board	Pregnancy
Indiscretion	Dietary noncompliance
Insulin deficiency	Noncompliance with insulin; pump failure

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there are a number of DKA cases in type 2 diabetics with no apparent underlying cause that are being increasingly recognized, termed *ketosis-prone type 2 diabetes*. This entity has also been described with several other terms, including *type 1.5 diabetes* and *Flatbush diabetes*.[3] This entity appears to be particularly common among black and Hispanic patients. Although these patients tend to present acutely (as type 1 diabetics with DKA), after treatment, most will not require long-term insulin.[1]

Differential Diagnosis

Hyperglycemia is a common presentation to the ED, particularly among diabetics with poor disease control. Most of these patients, however, will not have DKA or HHS. These patients can be distinguished from those with more severe hyperglycemic emergencies (DKA/HHS) by calculating an anion gap, measuring pH, and measuring serum osmolality. Additionally, hyperglycemia is frequently observed in patients with other critical illnesses, due to release of catecholamines and cortisol.[10] This so-called "stress hyperglycemia" shares many of the same neuroendocrine mediators as DKA and HHS, but patients do not develop a profound ketoacidosis and do not become significantly hyperosmolar.

There are several other conditions that can also present with ketosis, including alcoholic ketoacidosis (AKA), starvation ketoacidosis, and toxic alcohol ingestion. **(See Table 2.)** In AKA, patients often have elevated levels of ketone bodies, especially beta-hydroxybutyric acid (usually much greater than DKA patients), but they rarely have significantly elevated glucose levels. Patients with starvation ketosis also present with ketoacidosis, but like AKA patients, they rarely have hyperglycemia or serum bicarbonate concentration < 18 mEq/L. Patients who have ingested isopropyl alcohol (rubbing alcohol) also may have elevated levels of ketone bodies with a high osmolar gap, but these patients are typically hypoglycemic rather than hyperglycemic.[3]

Other causes of wide-gap acidosis should also be considered in ED patients presenting with a wide-gap acidosis and hyperglycemia (recall the "MUDPILES" mnemonic). **(See Table 3.)**

Table 2. Common Causes of Ketoacidosis

Condition	Blood Glucose Level
Diabetic ketoacidosis	Elevated
Alcoholic ketoacidosis	Normal or low
Starvation ketoacidosis	Normal or low
Isopropyl alcohol ingestion	Low to normal

Prehospital Care

Prehospital care of hyperglycemic emergencies is somewhat limited, though early identification of critically ill patients and those with time-sensitive comorbidities is critical. All diabetic patients and those with altered mental status should have their blood glucose checked in the field. Those with hyperglycemia > 500 mg/dL should have intravenous (IV) access obtained and receive an IV fluid bolus of 500 mL to 1000 mL of isotonic fluid if there are no signs of volume overload. A 12-lead electrocardiogram (ECG) should be performed to evaluate for signs of ischemia, infarction, or hyperkalemia in older patients and/or those who appear critically ill. Similarly, a stroke screening examination should also be performed. Insulin should **never** be administered without confirming a potassium level. Since potassium levels are rarely available in the prehospital setting, insulin administration in the field is extremely dangerous and must be avoided.

Emergency Department Evaluation

History

Key to the history in patients with hyperglycemia is screening for potential precipitating causes. First, rule out the most time-critical causes by asking about symptoms of acute coronary syndromes (ACS), including whether the patient has had any chest pain or shortness of breath, or any "atypical" ACS symptoms such as weakness and nausea. Be mindful, however, that diabetics with ACS may not manifest the typical symptoms of ACS and may complain of nonspecific symptoms.[11] Ask questions that screen for stroke, including numbness, weakness, vision changes, slurred speech, facial droop, and ataxia. Screen for infection with questions regarding recent fever or illness, dysuria, cough, and pathologic skin changes such as skin erythema or tenderness.

Patients with hyperglycemic emergencies, particularly DKA, often complain of gastrointestinal symptoms such as abdominal pain and vomiting.

Table 3. Differential Diagnosis of Wide Anion-Gap Metabolic Acidosis ("MUDPILES")

M	Methanol
U	Uremia
D	Diabetic/alcoholic/starvation ketoacidosis
P	Propylene glycol, acetaminophen/ paracetamol, phenformin/ metformin
I	Iron, isoniazid, inborn errors of metabolism
L	Lactic acidosis
E	Ethylene glycol
S	Salicylates, solvents

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Ketones have a paralytic effect on smooth muscle cells, which may lead to gastric retention and profuse vomiting, as well as a distended bladder. The presence of abdominal pain in HHS is much more likely to represent actual underlying pathology.

During the review of systems, ask about polyuria and polydipsia, as both frequently occur in both DKA and HHS. Polyuria occurs due to an osmotic diuresis that creates significant dehydration and leads to polydipsia. Finally, women of childbearing age should be asked about their last menstrual period and the possibility of pregnancy.

An accurate medication history can be helpful in the management of the diabetic emergency. Medications known to trigger hyperglycemic emergencies include corticosteroids, antipsychotics, thiazides, and SGLT2 inhibitors. Euglycemic DKA can also occur with SGLT2 inhibitor use. Cocaine use is also a known independent risk factor for DKA.[12] If the patient utilizes insulin, it is important to understand how it is administered and how frequently it is administered. If the patient has an insulin pump, inquire about any recent alarms. Common causes of DKA in insulin pump users include kinking of the tubing and leakage of insulin at the delivery site.[13,14] Turning off a patient's insulin pump is prudent in diabetic emergencies when the patient will be started on insulin in the ED.

Physical Examination

As with any critically ill patient, the physical examination should focus first on stabilization. The most critically ill diabetic patient may present with hypotension, shock, and signs of dehydration, including tachycardia, poor skin turgor, and dry mucous membranes. Clinicians may notice an odor of acetone in DKA patients, which has been described as "rotten fruit."

While vital signs are being obtained, perform a quick neurological examination, focusing first on mental status and signs of stroke. Approximately half of patients with DKA will present with lethargy and stupor.[2] In DKA, acidosis appears to play a key role in altered sensorium, as does hyperosmolarity, which have a synergist effect in mental status decline.[15]

Altered mental status and coma are much more common in HHS. Focal neurological deficits, even in the absence of stroke, have also been reported in HHS and are almost always associated with a change in mental status.[16] Thus, new focal deficits with intact sensorium should be assumed to be a stroke until proven otherwise. Seizures, often focal, are also seen in HHS.

A full set of vital signs, including temperature, should be obtained. While infection commonly precipitates hyperglycemic emergencies, these patients may not always present with a fever. In fact, due to peripheral vasodilation that often occurs in these conditions, patients may be normothermic or even hypothermic, particularly if they have overwhelming infection or are immunocompromised. Although not well studied, hypothermia is reported to be a poor prognostic sign in DKA.[1] Oral thermometers are notoriously inaccurate when tachypnea is present, as is often the case in DKA patients with Kussmaul respirations. One prospective trial evaluated 310 patients with tachypnea and found a 0.5°C oral temperature difference for every increment of 10 in the respiratory rate.[17] Obtaining a rectal temperature will provide a more accurate reading in these situations.[18]

A subsequent head-to-toe physical examination is key to avoid missing any precipitating causes. Particular focus should be given to the lungs, evaluating for signs of pneumonia, and to the skin, including intertriginous areas, looking for signs of cellulitis or other soft-tissue infections, including necrotizing fasciitis. Examine the genitalia for signs of Fournier gangrene and consider a rectal examination for perianal and perirectal abscess, as these are sources of infection that are easily missed in diabetics if not considered.[19] There are not good data reporting the incidence of skin infections as a precipitating cause, though anecdotal reports are common.

The abdominal examination is also essential, but must be interpreted with caution. Nausea, vomiting, and diffuse abdominal pain are common in DKA. In fact, more than half of DKA patients will have these complaints on arrival. The examination may even mimic that of an acute abdomen. Abdominal pain in DKA is correlated with severity of metabolic acidosis and is unrelated to the degree of hyperglycemia or dehydration. In a retrospective study of 189 DKA patients with abdominal pain, the average serum bicarbonate value was 9 mmol/L versus 15 mmol/L in those without abdominal pain, and 86% of patients with bicarbonate < 5 mEq/L had abdominal pain. Patients with DKA with a history of alcohol and cocaine use were also found to have an increased incidence of abdominal pain without underlying pathology.[19] Nonetheless, some patients with DKA and abdominal pain may have an underlying issue causing their pain, such as cholecystitis, appendicitis, pancreatitis, or other intra-abdominal infection or catastrophe. If acidosis is improving with therapy but the abdominal examination is not, further workup for underlying pathology should be performed.[1] Be cautious in abdominal pain patients with serum bicarbonate > 10 mEq/L and patients aged > 40 years, as they are more likely to have underlying pathology.[20]

In HHS, on the other hand, abdominal pain is rarely, if ever, due directly to the metabolic derangements of HHS and likely represents a precipitating cause. Thus, these patients require additional workup.[1,19]

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Finally, in patients with an insulin pump, inspect the tubing for evidence of kinking and inspect the pump site for signs of dislodgment and leakage of insulin.

Diagnostic Studies

Some diagnostic studies are required in all patients with suspected DKA/HHS, whereas others are situation-specific. **(See Table 4.)**

During the initial workup, DKA patients can be classified according to disease severity based on pH, bicarbonate levels, and mental status. **(See Table 5.)**

Bedside Studies

Point-of-Care Glucose

A point-of-care glucose level should be obtained for all ill diabetic patients and for any patient with altered mental status. Levels higher than approximately 200 mg/dL should prompt consideration and further workup for DKA/HHS.

Electrocardiogram

An ECG should be obtained early in older patients and patients of any age who appear ill, to screen for evidence of ischemia as well as for signs of electrolyte abnormalities. Specifically, look for signs of hyperkalemia, such as peaked T waves, new bradycardia, or widening of the QRS, as hyperkalemia often occurs early in DKA before insulin therapy is begun. More rarely, patients may present with hypokalemia, which may also be detected on ECG via flat T waves, a prolonged QT interval, or U waves.

Laboratory Testing

Diagnostic criteria for DKA and HHS are based on laboratory evaluation. DKA patients are (usually) hyperglycemic, ketonemic, and have a metabolic acidosis. The pH will be < 7.3, anion gap > 10, and serum bicarbonate < 18 mEq/L. Urine and serum ketones will be elevated.

Patients with HHS will not have ketoacidosis and typically do not have a large anion gap acidosis unless they have an alternative cause of acidosis (such as lactic acidosis). The key finding in HHS is elevated serum osmolality > 320 mOsm/kg (though it is usually much higher). **(See Table 6.)**

Chemistry Panel

The basic metabolic panel is key to distinguishing DKA and HHS, identifying electrolyte abnormalities, determining degree of disease severity, and driving therapeutic decisions regarding insulin and fluid administration. Serial chemistry panels should be obtained every 2 to 4 hours while a patient is on an insulin drip to monitor the anion gap and potassium levels.[1]

Anion Gap

The anion gap should be calculated. A gap > 10 is a diagnostic criterion for DKA. Usually, the gap will be much greater. Note, when calculating an anion gap, use the actual measured sodium level rather than the corrected level. As DKA is treated with insulin, the gap is expected to narrow and the sodium will usually normalize. The formula to calculate the anion gap is: $[Na^+] - ([Cl^-] + [HCO_3^-])$

Table 4. Initial Diagnostic Workup for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Recommended for all Patients

- Chemistry panel
- Venous blood gas
- Serum osmolality
- Urinalysis
- Complete blood cell count
- Bedside glucose

Situation-Dependent

- 12-lead electrocardiogram
- Lipase
- Blood and urine cultures
- Serum beta hydroxybutyrate (if available)
- Troponin
- Lactic acid
- Pregnancy test
- Urine drug screen

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Table 5. Diabetic Ketoacidosis Severity[1]

Severity	pH	Bicarbonate	Mental Status
Mild	7.25-7.30	15-18 mEq/L	Alert
Moderate	7.00-7.24	10-15 mEq/L	+/- Alert/drowsy
Severe	< 7.0	< 10 mEq/L	Stupor or coma

Table 6. Key Laboratory Findings in DKA Versus HHS[1]

Condition	Anion Gap	pH	Serum Bicarbonate	Serum Osmolality	Urine Ketones
DKA	> 10	< 7.3	< 18 mEq/L	Normal or mildly elevated	Positive
HHS	Usually normal	Normal (or mildly decreased)	Normal	> 320 mOsm/kg	Trace or no ketones

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

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Potassium

DKA and HHS patients have substantial total body potassium deficits due to osmotic diuresis. On average, deficits are usually 3 to 5 mEq/kg.[21] Despite these large deficits, DKA patients may appear hyperkalemic on presentation due to transmembrane shift of potassium into the extracellular space caused by their acidosis, hypertonicity, and insulin deficiency.

Sodium

Most hyperglycemic patients will have some degree of hyponatremia due to the osmotic shift of fluid from the intracellular to the extracellular space as a result of hyperglycemia. However, some patients may have an unexpectedly normal or even elevated sodium for the degree of hyperglycemia. These patients have a significant free-water deficit. To calculate expected serum sodium in the presence of hyperglycemia, the simplest formula is to expect an approximate 2 mEq/L drop in sodium for every 100 mg/dL increase above 100 mg/dL. For accurate calculation of adjusted sodium in a patient with hyperglycemia, use a corrected serum sodium calculator to determine the patient's serum sodium with the dilutional effect of hyperglycemia eliminated.

An online tool for calculating corrected sodium in hyperglycemia is available at: www.mdcalc.com/sodium-correction-hyperglycemia

Blood Gas

Serum pH is a diagnostic criterion for DKA and helps distinguish DKA from HHS. Traditionally, arterial blood gas (ABG) measurements have been used to determine serum pH, and current guidelines still suggest ABG analysis.[1] However, obtaining an ABG requires a painful procedure that is not without some risk, including arterial bleeding and nerve damage. Ma et al investigated whether ABGs provided useful information that was not available from venous blood samples and found that venous pH correlated very strongly with arterial pH (r = 0.95). Based on this study, the venous pH would typically be less than the arterial pH by an average of 0.015 (confidence interval [CI], ± 0.006 pH units).[23] ABG analysis changed diagnosis in 1% of patients, changed treatment in 3.5% of patients, and changed disposition in only 1% of patients. [23] For most patients, emergency clinicians can forego ABG testing during evaluation of hyperglycemic emergencies and can instead use the venous blood gas (VBG) to determine serum pH unless the patient is in profound hypovolemic shock.

Serum Osmolality

An effective serum osmolality > 320 mOsm/kg is a diagnostic criterion for HHS. DKA patients may also have elevated serum osmolality, but not usually to the same degree as HHS patients. When DKA patients have elevated serum osmolality in the presence of severe acidosis, they usually have concurrent changes in mental status, and their presentation may have an overlapping HHS component. Effective osmolality can be calculated by the following formula: (measured Na (mEq/L) x 2) + (glucose (mg/dL)/18). (Note, urea is not part of the formula, as it is freely permeable across the cell membrane and does not create a substantial osmotic gradient).[3]

Ketones

The presence of urine or serum ketones is a requirement to diagnose DKA. HHS patients may also have mildly elevated ketones. The major ketone body present in DKA is beta-hydroxybutyrate, but the traditional nitroprusside reaction test used by most laboratories to detect ketones does not measure it. The nitroprusside reaction test does detect acetone and acetoacetate with high sensitivity, but these are present in much lower levels than beta-hydroxybutyrate. Therefore, this test could underestimate the severity of ketoacidosis. If available, order a serum level of beta-hydroxybutyrate.

Complete Blood Cell Count

A mild leukocytosis (10,000-15,000 mm^3) is very common in DKA, even without concomitant infection. Elevated stress hormones, including cortisol and epinephrine, likely play a role. However, white blood cell counts > 25,000 cells/mm^3 should prompt a diligent search for possible infectious sources.[1] Additionally, a retrospective study of 153 ED patients with DKA found that band neutrophils > 10 predicted coexisting major occult infection with a sensitivity of 100% and a specificity of 80%.[24]

Urinalysis

Urinalysis can provide useful information regarding the presence of ketones as well as the presence of infection. In fact, urinary tract infection is one of the most common precipitants of DKA/HHS.

Cultures

Because infection is one of the most common precipitants of DKA and HHS, blood and urine cultures should be considered for any patient in whom infection is a possibility, particularly when fever is present.

Amylase and Lipase

Both amylase and lipase will be elevated in up to 25% of DKA patients, even in the absence of pancreatitis.[25] Therefore, hyperamylasemia and hyperlipasemia are nonspecific (even when > 3 times the upper

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limit of normal) and cannot be used alone to diagnose pancreatitis.[25] In uncertain situations, history and imaging may prove more useful than elevated pancreatic enzyme levels. The source of elevated pancreatic enzymes in the absence of acute pancreatitis is not definitively known. Several hypotheses for this exist, including decreased renal clearance, extrapancreatic sources from the gastrointestinal tract, leakage from pancreatic acini from neural and metabolic disturbances, among others.[25,26]

Imaging

Obtaining a chest x-ray early in treatment is helpful to exclude pneumonia as a precipitating cause if there is any concern for an infectious etiology such as cough, unexplained hypoxia, or fever.

Other imaging should be obtained, as needed, to exclude other precipitating causes. For example, consider head computed tomography (CT) for altered patients or abdominal CT for patients with findings concerning for an acute abdomen.

Treatment

Treatment of DKA and HHS centers around volume repletion, correction of hyperglycemia, and electrolyte replacement. There are 5 therapies that should be considered: (1) IV fluids; (2) insulin; (3) potassium; (4) phosphate; and (5) sodium bicarbonate. **(See Table 7.)** Underlying causes should be treated simultaneously.

IV fluids and insulin are mandatory in all patients, but phosphate and sodium bicarbonate are indicated more selectively. In general, the pace of therapy should match the pace of disease onset. That is, abnormalities in HHS (which have a more insidious onset than DKA, over days to weeks) can generally be corrected more slowly than DKA abnormalities, which tend to develop over hours to a few days.

Intravenous Fluids

IV fluids are utilized to replenish the tremendous fluid losses that occur in hyperglycemic emergencies, not to "wash out" ketone bodies, which instead are eliminated through pathways driven by insulin administration. In DKA, fluid deficits are approximately 3 to 5 L in mild cases and 5 to 6 L in severe cases, and estimated to average 70 mL/kg in children. In HHS, deficits may be as high as 9 to 12 L in adults and 12% to 15% of body weight in children. However, total replenishment will occur during the first 24+ hours and does not need to occur in the ED.

The First Hour

In the initial resuscitation, consider the patient's hemodynamic status. In a hemodynamically unstable patient, IV fluids should be administered as rapidly as possible. When the patient has no further signs of shock, to restore adequate perfusion, fluids should be administered at 15 to 20 mL/kg/hr, or in the average adult, 1 to 1.5 L/hr. The IV bolus can be started while awaiting the serum potassium level results. Initial fluid resuscitation decreases hyperglycemia 35 to 70 mg/dL, even without insulin, and increases the effectiveness of insulin and decreases counterregulatory hormones.[3,27] Therefore, provide volume resuscitation before starting insulin therapy.

Ongoing Rehydration

After adequate perfusion is restored, use corrected serum sodium levels to determine which type of fluid to administer. If corrected serum sodium is normal or elevated, ADA guidelines recommend using 0.45% saline (half-normal saline) at a rate of 250 to 500 mL/hr. British guidelines, however, recommend continuing normal saline throughout the resolution of DKA.[28] Therefore, some emergency clinicians may choose to continue isotonic fluids initially in patients whose corrected serum sodium is normal. There are not currently any prospective trials to support switching from isotonic to hypotonic fluids. If the corrected serum sodium is low, always continue isotonic fluids to avoid worsening hyponatremia.

Due to such large volume deficits, it is tempting to run fluids very aggressively following the initial bolus. However, administering fluids at a rate of 250 to 500 mL/hr is usually adequate. Adrogué et al prospectively compared the effects of managing DKA with aggressive versus nonaggressive fluid repletion in 23 patients. The aggressive fluid group received normal saline at 1000 mL/hr for 4 hours, followed by normal saline at 500 mL/hr for 4 hours. The nonaggressive group received normal saline at half the above rates (500 mL/hr for 4 hours followed by 250 mL/hr for the following 4 hours). Patients in the less-aggressive fluid group achieved a prompt and adequate recovery and maintained higher serum bicarbonate levels.[29]

Current recommendations for fluid therapy in HHS are similar as for DKA. However, be very careful not to overload HHS patients, who tend to be older and have more comorbidities (such as heart failure), and may not tolerate either the recommend-

Table 7. Five Treatments for Hyperglycemic Emergencies

Recommended Treatment for all Patients

- Intravenous fluids
- Insulin
- Potassium (after serum levels obtained)

Treatments to be Considered in Some Circumstances

- Phosphate
- Sodium bicarbonate

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ed large fluid bolus or the constant infusion rate of 500 mL/hr. Bedside ultrasound to assess volume status may be useful in these situations.

Which Crystalloid is Best? Normal Saline Versus Balanced Crystalloids

The current ADA consensus statement continues to recommend 0.9% ("normal") saline as the fluid of choice for treatment in DKA/HHS. However, several recent smaller studies suggest normal saline may not be the ideal fluid choice. Mahler et al randomized 45 patients to receive normal saline or balanced electrolyte solution (BES) (PLASMA-LYTE A®, Baxter International, Deerfield, IL). The group that received the BES had lower serum chloride and higher serum bicarbonate at resolution.[6] Chua et al retrospectively evaluated 23 patients who received PLASMA-LYTE 148® versus saline. The PLASMA-LYTE 148® group had faster resolution of metabolic acidosis, less hyperchloremia, and improved urine output. There was no difference in duration of intensive care unit (ICU) stay or glycemic control.[30] Both studies suggest that the avoidance of hyperchloremic metabolic acidosis caused by normal saline is likely the primary reason for the results.

Van Zyl et al performed the only randomized trial, to date, comparing lactated Ringer's (LR) solution to normal saline in adults. This study of 57 patients found a trend toward shorter time to venous pH normalization in the LR group compared to the normal saline group (540 min vs 683 min); however, this was not statistically significant. There was no significant difference in time to resolution of DKA.[7] The authors of the study concluded that it failed to indicate benefit for LR; however, one has to wonder whether these trends would become significant if the study were larger. A recent retrospective study looked at nearly 50,000 pediatric patients with DKA (88% of whom received normal saline; 12% received either LR alone or LR and normal saline). Both groups had similar length of hospital stay. The LR group was associated with lower costs ($1160 less on average). Interestingly, the LR group had lower rates of cerebral edema, at 12.7 cases/1000 episodes compared with the normal saline group, which had 34.6 cases (difference, -21.9; 95% CI, -30.4 to -13.3).[31]

Finally, a recent randomized trial with 15,802 critically ill patients found that patients who received balanced crystalloids (LR or BES) had a lower rate of new renal-replacement therapy, persistent renal dysfunction, and death from any cause compared with those patients who received normal saline.[32] Subgroup analysis with DKA patients has not yet been published. Taken together, available data seem to suggest an advantage to using balanced crystalloids instead of normal saline; however, at the current time, there is no definitive proof as to which fluid is better.

Adding Dextrose to Fluids

In DKA, once insulin is started, serum glucose will fall faster than ketoacidosis improves. On average, it takes approximately 12 hours for ketoacidosis to resolve, but only 6 hours for hyperglycemia to correct. In order to reverse catabolic pathways, insulin must be continued despite normalizing glucose levels. Eventually, glucose will need to be added to administered fluids to avoid hypoglycemia and to provide an energy source for ketone metabolism. Once serum glucose reaches 200 to 250 mg/dL, switch to dextrose-containing fluids. Generally, 5% dextrose in half-normal saline at 150 to 250 mL/hr provides an adequate glucose source.

Insulin

Insulin is a mandatory treatment in both DKA and HHS patients due to the presence of an absolute and/or relative insulin deficiency. With no insulin present in DKA, a catabolic state is created. Breakdown of proteins and fats occurs, resulting in ketone production and acidosis. Glucose is not able to enter intracellularly, and hyperglycemia develops. Prior to the development of exogenous insulin, DKA was universally fatal. In HHS, there is only a relative deficiency of glucose. That is, there is enough insulin to prevent the catabolic state and thus acidosis, but not enough to move glucose across cell membranes. Thus, hyperglycemia without acidosis develops.

Insulin is an anabolic hormone with 5 major actions: (1) driving glucose into the cell; (2) driving potassium into the cell; (3) reversing catabolism; (4) blocking the breakdown of fatty acids; and (5) block-ing the breakdown of proteins into ketone bodies. Before insulin is administered, it is imperative that the serum potassium level is known, because insulin will drive potassium into the cell, which could result in life-threatening hypokalemia with resultant arrhythmias. Do not start insulin unless the potas-sium level is > 3.3 mEq/L. Additionally, it is prudent to begin initial fluid resuscitation before insulin is started, especially in patients with poor perfusion. Administering insulin before fluids in hypotensive patients may worsen circulatory collapse.[3]

Bolus Versus Drip

How much insulin is to be given and by which route has been the subject of debate. Current ADA guidelines recommend starting an IV loading dose of 0.1 units/kg regular insulin followed by a continuous infusion of regular insulin at 0.1 units/kg/hr.[1] The guidelines also offer an alternative of a slightly higher dose of 0.16 units/kg/hr without a bolus. Indeed, the utility of the bolus has recently been called into question. Goyal et al prospectively compared the utility of the initial insulin bolus in 157 patients. Both groups were similar at baseline and received the same amount of IV fluids, and both

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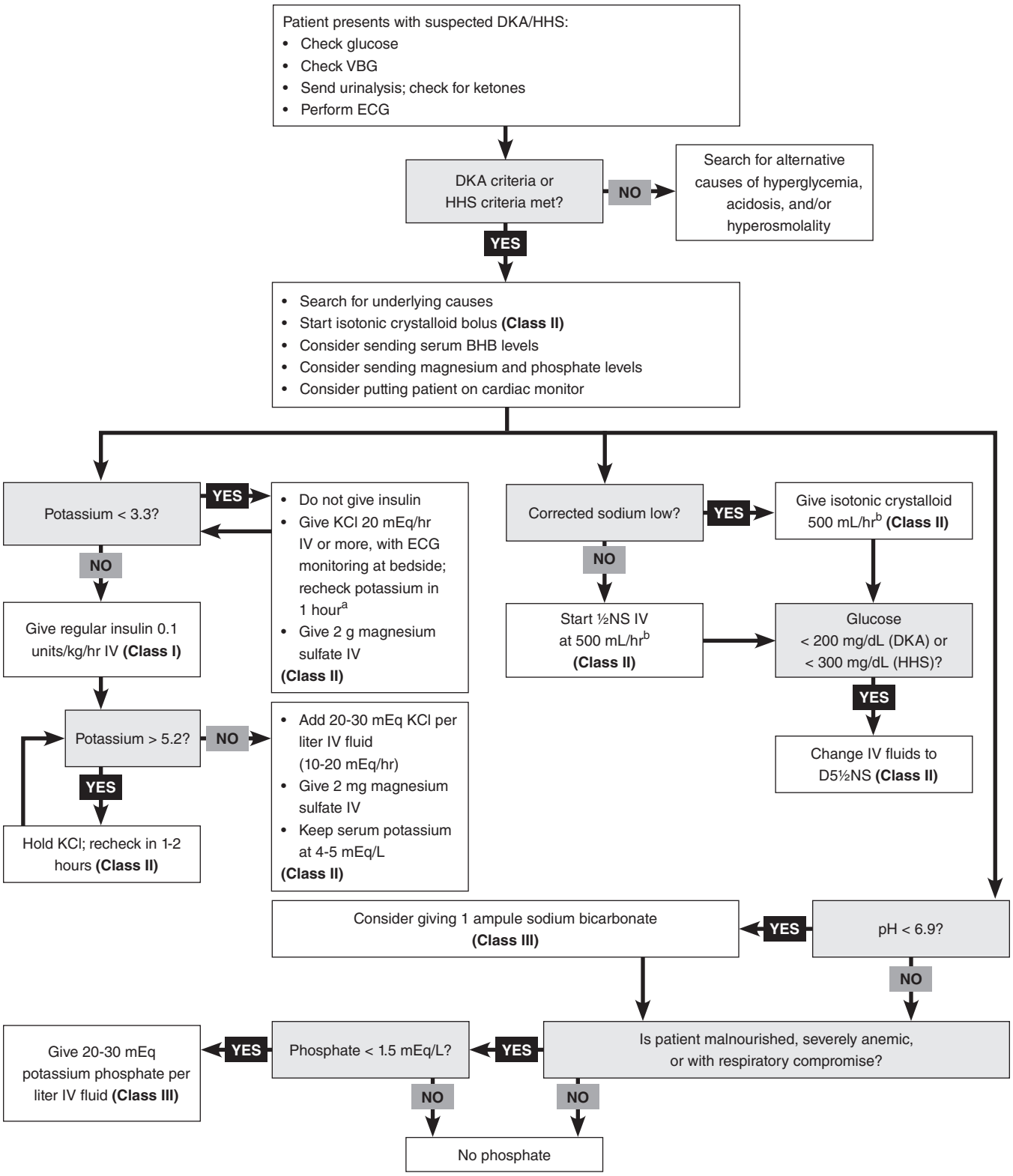
Clinical Pathway for Emergency Department Management of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State


Patient presents with suspected DKA/HHS:
• Check glucose
• Check VBG
• Send urinalysis; check for ketones
• Perform ECG
DKA criteria or HHS criteria met?
NO
Search for alternative causes of hyperglycemia, acidosis, and/or hyperosmolality
YES
• Search for underlying causes
• Start isotonic crystalloid bolus (Class II)
• Consider sending serum BHB levels
• Consider sending magnesium and phosphate levels
• Consider putting patient on cardiac monitor
Potassium < 3.3?
YES
• Do not give insulin
• Give KCl 20 mEq/hr IV or more, with ECG monitoring at bedside; recheck potassium in 1 hour[a]
• Give 2 g magnesium sulfate IV
(Class II)
NO
Give regular insulin 0.1 units/kg/hr IV (Class I)
Potassium > 5.2?
NO
• Add 20-30 mEq KCl per liter IV fluid (10-20 mEq/hr)
• Give 2 mg magnesium sulfate IV
• Keep serum potassium at 4-5 mEq/L
(Class II)
YES
Hold KCl; recheck in 1-2 hours (Class II)
Corrected sodium low?
YES
Give isotonic crystalloid 500 mL/hr[b] (Class II)
NO
Start ½NS IV at 500 mL/hr[b] (Class II)
Glucose < 200 mg/dL (DKA) or < 300 mg/dL (HHS)?
YES
Change IV fluids to D5½NS (Class II)
pH < 6.9?
YES
Consider giving 1 ampule sodium bicarbonate (Class III)
NO
Is patient malnourished, severely anemic, or with respiratory compromise?
YES
Phosphate < 1.5 mEq/L?
YES
Give 20-30 mEq potassium phosphate per liter IV fluid (Class III)
NO
NO
No phosphate

[a]Follow individual hospital guidelines for potassium infusion rates.

[b]Use lower rates for mild cases or if patient at risk for volume overload.

Abbreviations: ½NS, half-normal (0.45%) saline; BHB, beta-hydroxybutyrate; D5½NS, 5% dextrose in 0.45% [half-normal] saline; DKA, diabetic ketoacidosis; ECG, electrocardiogram; HHS, hyperosmolar hyperglycemic state; IV, intravenous; KCl, potassium chloride; VBG, venous blood gas.

For Class of Evidence definitions, see page 11.

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received insulin infusions. There was no significant difference in the incidence of hypoglycemia, rate of serum glucose change, anion gap change, or length of ED or hospital stay.[8] This study suggests the insulin bolus does not change clinically relevant endpoints. There are currently no data that show benefit of an insulin bolus, and doing so may result in more episodes of hypoglycemia. While the bolus does remain an option in current adult guidelines, it is specifically recommended against for pediatric patients.[5] For more information on management of pediatric patients, see the "Special Populations and Circumstances" section on page 12.

For patients in HHS, similar to recommendations for DKA patients, administer insulin at 0.05 to 0.1 units/kg/hr. Monitor glucose levels to prevent rapid falls. In general, keep glucose between 150 to 200 mg/dL in DKA and 200 to 300 mg/dL in HHS. In some cases, this necessitates dropping the insulin infusion rate to 0.02 to 0.05 units/kg/hr.

Transitioning Off the Insulin Infusion

In DKA and HHS, it typically takes several hours (> 12) for metabolic abnormalities to be corrected completely. Thus, it will not be a common occurrence for the emergency clinician to stop insulin infusions, except in mild cases or when ED boarding times are prolonged. In DKA, criteria for stopping the insulin drip include blood glucose < 200 mg/dL and at least 2 of the following conditions: (1) anion gap ≤ 12; (2) venous pH > 7.3; and (3) and serum bicarbonate ≥ 15 mEq/L. In HHS, osmolality and mental status should be normalized. Before the infusion is stopped, intermediate (NPH) or long-acting (detemir or glargine) subcutaneous insulin should be administered at least 2 hours before the insulin drip is stopped during an "overlap" period. This helps prevent recurrent hyperglycemia and acidosis because IV insulin has a very short half-life. If the patient has resumed oral intake, short-acting insulin should also be administered with meals.

Long-Acting Insulin

For patients who are already on long-acting insulin, some experts recommend administering the patient's long-acting insulin right away, during initial management, rather than waiting until the resolution of illness. Current British guidelines recommend continuing the patient's long-acting insulin (glargine, detemir, degludec) during IV infusion. Hsia et al conducted a prospective randomized trial of 61 patients in which the intervention group received glargine subcutaneous (0.25 units/kg) as soon as possible after starting IV insulin. The control group did not receive long-acting insulin initially. Decisions about subcutaneous transition (timing, doses, type) were left to the primary teams to replicate typical inpatient care. They found lower rates of rebound hyperglycemia in the group that received glargine (10/30) than the group that did not (29/31; $P = < .001$), without an increase in episodes of hypoglycemia.[33] Note that even when long-acting insulin is given up-front, shorter-acting subcutaneous insulin at the time of transition is still required.

Potassium

Patients with hyperglycemic emergencies can have large changes in serum potassium levels during treatment and require continuous cardiac monitoring. Though patients may present with hyperkalemia or hypokalemia initially, most will be either borderline or truly hyperkalemic, due to transmembrane shift of potassium into the extracellular space secondary to acidosis, insulin deficiency, and hypertonicity. Despite high serum potassium levels early on, both DKA and HHS patients actually have total body potassium deficits, due to osmotic diuresis. Thus, once insulin is begun and acidosis begins to be corrected, potassium levels can plummet.

Ideally, potassium should be maintained between 4 and 5 mEq/L. Keep in mind the average potassium deficit in DKA is 3 to 5 mEq/kg (approximately 200-350 mEq in the average-sized adult), so potassium repletion will need to be ongoing throughout treatment.

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Therapy is guided by initial serum potassium levels. Two key numbers to remember are: 5.2 mEq/L (the upper limit of normal) and 3.3 mEq/L (the lower limit of normal). For levels > 5.2 mEq/L, do not administer potassium, and begin insulin. Once the serum potassium level drops < 5.2 mEq/L, add 20 to 30 mEq potassium chloride per liter of fluid (administering approximately 10-20 mEq/hr). For serum potassium level < 3.3 mEq/L, hold insulin and give potassium chloride 20 mEq/hr or more. **(See Table 8.)** To ensure best patient outcomes, the following cautions should be observed:

- Be aware of your hospital's guidelines for potassium infusion rates, as these may vary dosage.
- Ensure that patients receiving potassium infusions are on continuous cardiac monitoring.
- Remember to monitor serum potassium level every 2 to 4 hours while the patient is on an insulin drip. Failure to adequately replete potassium after a patient is "stabilized" on an insulin drip is a known cause of cardiac arrest in DKA, due to hypokalemia-induced arrhythmias.
- All patients who are hypokalemic are also hypomagnesemic. Always replete magnesium in hypokalemic patients as long as renal function is intact. The usual dose is 2 g magnesium sulfate IV.

Sodium Bicarbonate

While it is tempting to give sodium bicarbonate to treat acidosis in DKA due to its theoretical benefits, data have not supported this practice for most patients, as sodium bicarbonate has many potential drawbacks. Potential adverse effects of sodium bicarbonate include hyperosmolarity, hypernatremia, blood-brain disequilibrium, and central nervous system hypercarbic respiratory acidosis. Thus, sodium bicarbonate should be used very selectively, in the sickest patients. A handful of small prospective randomized studies and many retrospective studies have looked at sodium bicarbonate administration in patients with pH > 6.9 and found no benefit.[34-39] A 2011 systematic review of 44 studies also came to similar conclusions.[40] No prospective studies have been performed in patients with pH < 6.9.

Currently, sodium bicarbonate is recommended only in patients with severe acidosis (pH < 6.9) who are at risk for myocardial and central nervous system depression without reversal of their acidosis. Sodium bicarbonate may also be useful in acidotic patients who present with hyperkalemic emergencies. Sodium bicarbonate should be avoided in pediatric patients, because retrospective studies have shown it to be associated with increased risk for cerebral edema.[40,41] Sodium bicarbonate is not used in patients with HHS.

Table 8. Recommended Potassium Replacement in the First Hours of Diabetic Ketoacidosis

Serum Potassium (mEq/L)	Replacement Dosing*
> 5.2 (hyperkalemia)	Hold potassium, start insulin, recheck in 1 hour
4.0-5.2 (goal potassium range)	10 mEq/hr, recheck in 1 hour
3.3-4.0 (hypokalemia)	10-20 mEq/hr, recheck in 1 hour
< 3.3 (severe hypokalemia)	20 mEq/hr or more, with hourly checks and adjustments based on response to therapy; hold insulin; monitor electrocardiogram at bedside

*Refer to individual hospital policy on dosing.

Phosphate

Several small studies have shown no proven benefit to routine administration of phosphate during treatment of DKA and HHS in adult patients. Phosphate is most likely to benefit patients with severely low phosphate (< 1.0-1.5 mg/dL) and in those with respiratory depression, cardiac dysfunction, cachexia, and anemia. If administering, give 20 to 30 mEq potassium phosphate (K_2PO_4) per liter. Use caution, as overly aggressive phosphate repletion can precipitate hypocalcemia. Pediatric hospitals often use potassium phosphate for some potassium repletion, and this may vary by institution.

Special Populations and Circumstances

Pediatric Patients

DKA/HHS management in children is similar to adults, but there are some key points that should be noted. Guidelines recommend that children receive at least 1 hour of IV fluids before insulin is initiated.[5] For children not in shock, administer 10 to 20 mL/kg over 1 to 2 hours. Fluids are expected to drop serum glucose and osmolality even without insulin administration. Thus, guidelines recommend starting IV fluids prior to insulin and monitoring the rate of glucose decline. Start insulin once plasma glucose is no longer falling with fluids alone (or falling < 50 mg/dL/hr). For children, guidelines recommend insulin be administered at 0.025 to 0.05 units/kg/hr (note this is a lower dose than for adults). Insulin should be titrated to allow a gradual reduction in glucose of approximately 75 to 100 mg/dL/hr.

Pediatric guidelines specifically recommend against an insulin bolus. One prospective randomized trial of 38 pediatric patients with DKA showed no significant difference in the decline in serum glucose level, changes in serum osmolality, degree of acidosis, or time to reach a serum glucose level of 250 mg/dL when an insulin bolus was given. The

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authors concluded that the bolus is unnecessary, as it does not offer any benefit.[42] Additionally, the ISPAD guidelines state that the bolus can potentially decrease osmotic pressure, thus potentially precipitating shock (though the above-mentioned study argues against this theory), may promote cerebral edema, and can cause hypokalemia. Therefore, current guidelines do not recommend an insulin bolus in children.[5]

Sodium bicarbonate is associated with cerebral edema and should be avoided unless absolutely necessary, such as in hyperkalemic emergencies and severe acidosis (pH < 6.9) with depressed cardiac contractility or imminent cardiac arrest.

Children are most at risk for cerebral edema, and careful monitoring should look for evidence of developing increased intracranial pressure. (See the following section, "Cerebral Edema.")

Avoid placing central venous catheters (CVCs) in children with DKA unless absolutely necessary, as they are associated with increased risk of thrombosis. In a retrospective study of 113 pediatric ICU patients with DKA, 6 required femoral CVC placement and 3 of them developed ipsilateral DVT requiring long-term anticoagulation. On average, these patients were younger, with a median age of 10 months. The number of DKA patients with deep vein thrombosis with a CVC in place was significantly greater than for all non–DKA patients with a femoral CVC.[43]

Cerebral Edema

Clinically apparent cerebral edema in DKA is much more common in children than in adults (though still < 1%), has a high mortality rate (21%-24%), and is responsible for the majority of deaths in pediatric DKA cases.[5] Cerebral edema usually develops shortly after beginning treatment (within the first 12 hours) but can occur up to 2 to 3 days later. Look for signs of elevated intracranial pressure such as headache, hypertension with bradycardia, changes in mental status, cranial nerve palsies, incontinence, posturing, and abnormal respiratory patterns. Mild headaches prior to initiation of treatment are common in DKA and should not be considered as part of the diagnosis for cerebral edema; however, a severe headache that develops after treatment is initiated is much more worrisome.

The pathogenesis of cerebral edema development is not clear, though it appears to occur more often in patients who are sicker on presentation (worse acidosis, higher serum urea nitrogen concentration, severe hypocapnia). Its development does not appear to be related to initial osmolality or osmotic changes during treatment.[2,44]

Previously, some literature suggested that rapid administration of IV fluid may contribute to cerebral edema; however, a recent large randomized trial showed no difference in frequency of cerebral edema in slower versus more rapid fluid administration groups.[45] In HHS, animal studies have suggested that a rapid decline in osmolality may contribute to cerebral edema. Therefore, most recommend keeping glucose levels near 300 mg/dL during treatment.[46]

Treatment for cerebral edema in DKA and HHS is mannitol 0.5 to 1 g/kg IV over 20 minutes. Repeat in 30 minutes if there is no improvement with the first dose; 3% hypertonic saline, 2.5 mL/kg or 3 to 5 mL/kg over 15 to 30 minutes can also be given as an alternative. Elevate the head of the bed in suspected cases, and do not delay treatment to obtain imaging. Obtain a head CT after initiation of treatment. Other complications that may present with similar symptoms include dural sinus thrombosis and stroke.[5]

Airway Management in Diabetic Ketoacidosis

Intubation of DKA patients should be avoided unless it becomes absolutely necessary. DKA patients have a significant metabolic acidosis, and they compensate for this by increasing their minute ventilation, allowing them to expire more CO_2. Even a short period of apnea during intubation can cause a precipitous drop in pH as CO_2 levels rise. Additionally, once intubated, it can be difficult to match the pre-intubation respiratory alkalosis of a hyperventilating patient. Eventually, acidosis can become so severe that circulatory collapse occurs. If intubation becomes absolutely necessary (sometimes due to such severe fatigue that a patient is unable to compensate with an adequate respiratory alkalosis), minimize apnea time. Use mask ventilation during periods of apnea. Optimize chances for first-pass success. If rapid sequence intubation becomes absolutely necessary, choose a short-acting paralytic such as succinylcholine, or rocuronium in hyperkalemic patients. Once intubated, use a ventilator mode that allows the patient to set the rate and tidal volume received, such as a pressure-targeted mode.[47]

Euglycemic Diabetic Ketoacidosis

DKA cannot be excluded based solely on a normal blood glucose level. Many cases of "euglycemic DKA," in which glucose is only mildly elevated (often around 250 mg/dL and sometimes less), have been reported.[48-51] The incidence of euglycemic DKA appears to be rising due to increasing use of a newer drug class, the SGLT2 inhibitors, in outpatient diabetes management. These drugs can be easily recognized on a medication list, as they all have the suffix "-gliflozin." Some of the most common include canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro™). They work therapeutically by increasing urinary excretion of glucose, thus improving glycemic control. However, these medications increase

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the risk of DKA, likely through several pathways, because they may also decrease renal clearance of ketone bodies, promote hepatic ketogenesis, and increase glucagon.[49,52] The exact mechanisms are still being elucidated.

When evaluating patients for DKA who are taking this class of drug, be certain to calculate an anion gap, obtain a pH, and look for urine ketones. Do not be falsely reassured by a normal glucose, particularly in a patient who appears ill. Due to relatively lower glucose levels on presentation for a DKA patient, dextrose may need to be added to fluids much earlier than in a more typical hyperglycemic DKA patient. Additionally, avoid an insulin bolus and consider a reduced dose of insulin. Of note, the United States Food and Drug Administration (FDA) recently released a warning that Fournier gangrene has been reported with this medication class. The risk of genital infections with this class is thought to be due to increased glycosuria.[53] The FDA recommends discontinuing SGLT2 inhibitors in any patient taking them who presents with Fournier gangrene.

There are a few other patient groups that may present with euglycemic DKA. These include pregnant patients, those who are fasting, and those who have administered insulin prior to arrival.[3] Again, be sure to look for a wide anion gap, low pH, and urine ketones.

Refractory Acidosis/Failure to Improve

In refractory acidosis, search diligently for occult underlying causes, particularly bowel ischemia, sepsis, or abscess. Administration of large volumes of IV normal saline has also been associated with prolonged acidosis due to the large amount of chloride present in saline, creating a hyperchloremic metabolic acidosis. Nonetheless, though their bicarbonate may be low, these patients should not have a wide gap acidosis from saline.

Dialysis Patients

Although dialysis patients are less likely than other diabetic patients to develop DKA, the incidence of DKA in this population group is rising. There are some key differences in their workup and management because they do not develop an osmotic diuresis, resulting in less volume and electrolyte loss. Dialysis patients may have a mixed metabolic acidosis with metabolic alkalosis due to high bicarbonate dialysate received during dialysis. This may result in a serum bicarbonate that is higher than expected in DKA. Calculate an anion gap to help make the diagnosis. During the treatment phase, dialysis patients may not require much, if any, fluids unless they have had a large amount of fluid loss from nonurinary sources (such as vomiting or diarrhea). If fluids are given, start with smaller volumes and monitor closely for evidence of volume overload. Insulin is given at usual doses. Be particularly cautious with potassium levels, as most will be hyperkalemic and will not require any potassium supplementation.[54,55]

Controversies and Cutting Edge

Intravenous Versus Subcutaneous Insulin

Currently, ADA and pediatric ISPAD guidelines recommend IV insulin as the preferred delivery route in DKA patients due to its short half-life and easy titration. However, some small studies in adults suggest that subcutaneous administration of insulin has similar outcomes when used in patients with mild to moderate DKA. Umpierrez et al randomized 45 DKA patients into 3 groups: (1) subcutaneous aspart insulin every hour; (2) subcutaneous aspart insulin every 2 hours; and (3) IV infusion of regular insulin. They found no difference in mortality, duration of treatment until correction of hyperglycemia or resolution of ketoacidosis, length of hospital stay, or number of hypoglycemic events. They concluded that subcutaneous insulin aspart given every 1 to 2 hours is safe and effective for uncomplicated DKA.[56] Similar studies have been performed with rapid-acting insulin lispro, with comparable results. **(See Table 9.)**

One major benefit of subcutaneous dosing is that it may allow patients with mild DKA who do not otherwise need ICU-level care to avoid an ICU admission. Still, subcutaneous administration requires frequent dosing (every 1 to 2 hours) and requires close glucose monitoring. Many hospital floors are unable to accommodate this dosing frequency (though it may be feasible on some stepdown units). Subcutaneous administration has been shown to reduce costs when it avoids an ICU admission. Note: subcutaneous administration is not recommended in severe DKA, including in patients with severe acidosis, hypotension, or altered mental status.

Table 9. Subcutaneous Insulin Dosing

Insulin Lispro 1-Hourly Dosing[57]

1. 0.3 units/kg of body weight, *then*
2. 0.1 units/kg/hr until glucose reaches 250 mg/dL (change IV fluid to D5½NS), *then*
3. 0.05-0.1 units/kg/hr until resolution of DKA

Insulin Aspart 2-Hourly Dosing[56]

1. 0.3 units/kg body weight, *then*
2. 0.2 units/kg 1 hour later, *then*
3. 0.2 units/kg q2h until glucose reaches 250 mg/dL, *then*
4. 0.1 units/kg q2h (change IV fluid to D5½NS) and continue until resolution of DKA

Abbreviations: D5½NS, dextrose 5% in half-normal (.045%) saline; DKA, diabetic ketoacidosis; IV, intravenous; q2h, every 2 hours.

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Risk Management Pitfalls for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State in the Emergency Department

1. **"He was very hyperglycemic, so I started insulin right away."**
   Starting insulin before the potassium level is known can result in dangerous arrhythmias, such as torsades de pointes, as insulin drives potassium into cells, lowering potassium further. A smaller percentage of patients will present with hypokalemia on arrival. Additionally, initiating volume resuscitation before giving insulin has several benefits, including decreasing serum glucose and restoring renal perfusion.

2. **"Her glucose is normal, so it can't be DKA."**
   Patients taking SGLT2 inhibitors may develop euglycemic DKA, in which glucose is much lower than typical DKA cases, often in the 150 to 250 mg/dL range. Other patient types who may present with euglycemic DKA include those who took insulin before arrival, pregnant patients, and patients with vomiting.

3. **"He was complaining of right-sided weakness, but I assumed it was from being so hyperglycemic."**
   While hyperosmolarity can cause neurological deficits, including focal deficits, patients with focal deficits from hyperosmolarity should also have changes in mental status. Assume stroke until proven otherwise.

4. **"HHS patients have 9 to 12 L of fluid deficit, so I didn't expect him to develop pulmonary edema with a few liters in the ED."**
   Though their deficits are almost always much larger than DKA patients, HHS patients tend to be older with more comorbidities. Generally speaking, their resuscitation should occur over days and should be less aggressive once initial perfusion is restored. Be especially careful in patients with a history of heart failure.

5. **"Her pH was low, so I gave her sodium bicarbonate."**
   Although sodium bicarbonate can raise pH quickly, it has a very high osmolarity and can cause a paradoxical central nervous system acidosis. It is the only treatment that can increase the incidence of cerebral edema in children, and has never been shown to be of any benefit in patients with pH values > 6.9. Be forced into giving it, never do so prophylactically.

6. **"Her mom gave a classic story of gastroenteritis. I never suspected DKA—the patient had no history of diabetes."**
   Children, particularly the very young, often present with nonspecific findings in DKA that are easy to mistake for other causes. In ill-appearing children, obtain a fingerstick glucose and urinalysis to look for ketones and glucosuria. Nausea/vomiting is a common initial presentation for DKA in children. Additionally, gastroenteritis is often a trigger for DKA in diabetic patients.

7. **"I thought the child was getting better with treatment; his blood pressure went up, his heart rate came down, and he went right to sleep."**
   Monitor children frequently for signs of cerebral edema including severe headache, changes in mental status, hypertension, and bradycardia.

8. **"He was breathing fast, so I intubated him to reduce his work of breathing and metabolic demands."**
   DKA patients have a respiratory alkalosis to compensate for their metabolic acidosis. Intubating these patients can be dangerous. During periods of apnea, their pCO_2 can rise rapidly. Additionally, after intubation it can be difficult to match pre-intubation minute ventilation. Avoid intubation unless it becomes absolutely necessary; for example, for airway protection or in cases where extreme fatigue is interfering with the patient's minute ventilation and ability to compensate for metabolic acidosis.

9. **"I thought his persistent acidosis was from DKA. I never thought it could be from another cause."**
   In patients whose glucose is falling but their acidosis is not improving despite appropriate therapy with insulin and fluids, look for alternative causes such as sepsis, bowel ischemia, and occult abscess.

10. **"I assumed his seizure was from HHS."**
    Seizures in HHS can occur, and may be focal, but they are much rarer in DKA. In either case, always check an immediate glucose in patients having seizures, especially those on an insulin drip, to rule out hypoglycemia as the cause.

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Thrombosis and Anticoagulation

Case reports have indicated an increased risk of thrombosis in hyperglycemic crises, particularly in HHS. In a retrospective study of 2859 patients, patients with hyperosmolarity had a significantly higher risk of venous thromboembolism than those with uncomplicated diabetes, and the risk is increased for several months after resolution of HHS. The risk was not increased in DKA patients.[58] Current British guidelines recommend prophylactic low-molecular-weight heparin in HHS patients throughout admission,[59] though this is not based on any prospective studies, and ADA guidelines do not include any recommendations on anticoagulation.

Disposition

With the exception of very mild cases, all patients with a hyperglycemic crisis require admission to the hospital. The level of care will be determined primarily by coexisting illnesses and whether the patient is on an insulin drip. Individual hospital policy usually determines the level of care required for insulin drip use (often the ICU). Patients with mild DKA who have responded well to initial resuscitation and who are receiving subcutaneous insulin may be appropriate for the floor or a stepdown unit. Some patients with mild DKA may be eligible for discharge home when their metabolic abnormalities have been corrected with subcutaneous insulin, the underlying causes have been addressed, and they are determined to be reliable and have a good follow-up plan. This is best done in consultation with the patient's endocrinologist.

Summary

DKA and hyperglycemic emergencies are relatively common presentations to the ED and require careful management. On arrival, secure the airway, breathing, and circulation, obtain an ECG, and perform a thorough examination and history, focusing particularly on underlying causes, such as infection. Obtain a broad laboratory workup, including VBG instead of ABG. Start volume resuscitation with isotonic fluids and measure serum potassium before starting insulin therapy. An insulin drip can be initiated without a loading dose. Subcutaneous insulin is an alternative only in mild or mild-to-moderate cases. Continue IV fluids using crystalloids, with consideration of the benefits provided by balanced crystalloids, and carefully monitor serum potassium and glucose during insulin infusion. Be prepared to add glucose to fluids as serum glucose decreases. Monitor patients for complications, including cerebral edema and hypokalemia. Avoid sodium bicarbonate, except in a few select circumstances.

Case Conclusions

In the first case, the young woman's medical record showed she had been admitted 4 times in the past year with DKA. You recognized that recurrent cases are often due to insulin noncompliance, and indeed the patient admitted she had not been taking her insulin because she thought it caused her to gain weight. Still, you looked for other underlying causes, including pregnancy and infections. You decided not to bolus her insulin because you knew it does not have any proven benefit. You knew she was not an appropriate patient for subcutaneous insulin administration due to her severe acidosis. You started her on a balanced electrolyte solution with the intent to avoid possible iatrogenic hyperchloremic metabolic acidosis that can be associated with normal saline. You did not give her any sodium bicarbonate when her pH resulted at 7.1. You decided against intubation because you knew her work of breathing was an effort to generate a respiratory alkalosis to offset her metabolic acidosis and you knew you would have difficulty matching her pre-intubation minute ventilation on a ventilator. You admitted her to the ICU, where she had an uneventful recovery.

The second case of the 76-year-old man was a typical presentation of HHS, which is usually seen in older patients and presents with progressive weakness, lethargy, and mental status decline. You recognized that patients with HHS are profoundly volume-depleted, and isotonic crystalloids should always be the initial fluids, to begin restoring euvolemia while awaiting serum chemistries. The initial therapy of HHS and DKA are exactly the same. HHS has volume deficits of 10 to 12 liters, which is essentially twice that of DKA. You recognized this patient's condition was associated with a much higher mortality than DKA, and you admitted him to the ICU.

The 30-year-old patient with type 1 diabetes was in DKA and required IV fluid volume, insulin, and potassium; this therapeutic approach would have been "perfect," assuming he had the expected serum potassium level seen in most patients in DKA. However, this patient's initial serum potassium on ED entry was 3.5 mEq/L, and treatment drove his serum potassium intracellularly, resulting in a prolonged QT-induced, life-threatening arrhythmia. Lesson learned—begin insulin only after a patient's potassium is known; similarly, never start potassium in DKA without knowing the initial serum potassium level. The patient was successfully cardioverted out of torsades de pointes, his insulin drip was stopped, and both potassium and magnesium were aggressively repleted.

Time- and Cost-Effective Strategies

- CT scans in DKA patients with abdominal pain are low yield, as most DKA patients present with abdominal pain due to acidosis. CT scan is indicated in patients who provide a history of intra-abdominal pathology as the precipitant of their illness, such as pain preceding their illness

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("I started with pain near my belly button that moved to my right lower quadrant"). Additionally, in patients whose pain does not improve as their acidosis improves, CT is indicated.
- For patients with mild DKA, subcutaneous insulin administration every 1 to 2 hours instead of an insulin drip may allow a patient to be admitted to a stepdown unit rather than the ICU, resulting in cost savings.
- Use VBGs instead of ABGs. They provide similar information and do not require any additional sticks.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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1. **A 17-year-old girl who administers her own insulin has presented with DKA 6 times in the past year. Which of the following is the most likely cause?**
   a. Insulin noncompliance
   b. Stroke
   c. Pneumonia
   d. Fournier gangrene

2. **An elderly patient with a history of diabetes, hypertension, and congestive heart failure presents with a blood glucose of 1100 mg/dL and serum osmolality of 350 mOsm/kg. Which of the following is the most appropriate initial action?**
   a. Obtain an electrocardiogram
   b. Begin insulin infusion
   c. Bolus 2 to 3 L of normal saline
   d. Give sodium bicarbonate

3. **An 80-year-old patient presents with serum glucose of 1100 mg/dL, anion gap of 14, and pH 7.34. His serum osmolarity is 352 mOsm/kg. He has trace urine ketones. He complains of severe abdominal pain and diffuse tenderness. In this situation, which of the following is TRUE?**
   a. His abdominal pain likely represents a precipitating cause.
   b. His abdominal pain is probably due to acidosis.
   c. His abdominal pain is probably due to hyperosmolarity.
   d. Abdominal pain is commonly due to HHS itself.

4. **A DKA patient is given an IV bolus of lactated Ringer's solution on arrival. His heart rate has improved and blood pressure has normalized. His corrected serum sodium level is elevated. Which of the following is the most appropriate fluid choice for ongoing rehydration?**
   a. Lactated Ringer's solution
   b. Balanced electrolyte solution
   c. Normal saline
   d. Half-normal saline

5. **A DKA patient has been receiving normal saline at 500 mL/hr for 2 hours and is on an insulin infusion at 0.1 units/kg/hr. Repeat labs show glucose of 180 mg/dL and the anion gap is 20. What is the most appropriate adjustment in therapy?**
   a. Stop the insulin infusion
   b. Begin transition to subcutaneous insulin
   c. Change fluid to 5% dextrose in half-normal saline
   d. Give 50% dextrose in water

6. **A 3-year-old child presents with DKA. Which of the following is associated with an increased risk of cerebral edema in this patient?**
   a. Insulin bolus
   b. Fluid bolus
   c. Use of lactated Ringer's solution
   d. Sodium bicarbonate administration

7. **Which of the following is the clearest indication for the use of sodium bicarbonate in DKA?**
   a. pH 7.0
   b. Bicarbonate 8 mEq/L
   c. Anion gap 28
   d. Potassium 8.0 mEq/L with widening of QRS

8. **Which of the following treatments for DKA patients is NOT given routinely?**
   a. IV fluids
   b. Insulin
   c. Phosphate
   d. Potassium

9. **A 28-year-old woman presents with DKA and is tachypneic to 30 breaths/min and febrile. Which of the following is an indication for intubation?**
   a. Impending airway obstruction
   b. Tachypnea
   c. Sepsis
   d. Confusion

10. **A diabetic patient presents with serum glucose of 180 mg/dL, pH 7.1, anion gap of 24, and highly elevated serum beta-hydroxybutyrate levels. Which of the following medications is associated with this condition?**
    a. Empagliflozin
    b. Metformin
    c. Glipizide
    d. Acarbose

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Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this activity, you should be able to: (1) identify common precipitants of diabetic ketoacidosis and hyperosmolar hyperglycemic state; (2) identify metabolic derangements indicative of hyperglycemic emergencies and determine strategies for correction; (3) select appropriate crystalloid and insulin rates for resuscitation and ongoing treatment; and (4) discuss indications for supplemental therapies, such as sodium bicarbonate and phosphate.

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